REMARKS

Claims 24-28, 41-45, 49 and 57-62 are under examination and have been rejected. In response, Applicants have amended claims and make the following remarks:

Drawings

Applicants have submitted herewith a new paper sequence listing and 3.5" diskette, along with a statement under 37 C.F.R. 1.821(g), containing sequences identified in the drawings and have amended the descriptions of drawings denoted as Figures 4A, 4B, 5A, 5B, 6A, 6B, 6D, 6E, 6F, 14 and 15 to include reference to said SEQ ID NOs. No new matter has been added.

Specification/Informalities

Applicants have amended the paragraph on page 1, to remove the lone parenthetical mark at line 24.

Applicants noted a misprint in the application as filed. Applicant has amended the paragraph on page 21, lines 10-25, of the application to remove the "boxes" at lines 12 and 17 and replaced these with the "μ" (micro) symbol. This adds no new matter since the correct symbol appears in the parent patent (U.S. 6,617,122 at column 11, lines 41 and 47, respectively).

Applicants similarly corrected a misprint at page 17, lines 8 and 9, of the application where boxes appear instead of the micro symbol. The micro symbol "μ" has been inserted therefor, which symbol also appears in the parent patent at column 9, lines 23 and 24, respectively).

Applicant has also amended the title of the application in accordance with the Examiner's suggestion.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 24-28, 41-45, 49 and 57-62 were rejected under 35 U.S.C. §112, ¶1, as failing to meet the written description requirement on grounds that they contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is a new matter rejection.

Claims 24, 27, 28, 61 and 62 were rejected as using the term "ABCA1 polypeptide" whereas the specification uses the term "ABC1 polypeptide." In response, Applicant has amended the rejected claims to recite the term "ABC1" in place of "ABCA1." In view of this amendment, Applicants believe that this ground of rejection has been overcome and respectfully request that it be withdrawn.

The Examiner also notes that claims 57-62 were added by preliminary amendment, with support cited at pages 1, 9 and 76. The Examiner contends that page 1 teaches a correlation between HDL-C and cardiovascular disease, that page 9 teaches a method for screening a compound for use in treatment of low HDL-C, and that page 76 "states that agents that modulate ABCA1 biological activity can be used to treat cardiovascular disease OR low HDL-C" apparently contradicting "applicant's assertion that this disclosure supports the claimed method." (see page 6 of the Office Action)

In response, Applicants have amended claims 57-62 to better reflect the invention. In addition, Applicants have amended claim 24, which is a linking claim, to recite that the method is drawn to increasing HDL-C in a mammal by administering an effective amount of a compound that increases ABC1-mediated lipid transport. This is supported in that the

application (at page 75, lines 20-24) teaches the correlation between ABC1 level and HDL level. In addition, page 1, line 26, teaches the beneficial effects of elevating HDL level. Claim 25 has now been amended to recite that the cardiovascular disease recited in claim 24 is associated with low HDL-C in the mammal. Applicants also direct the Examiner's attention to page 1 of the application, teaching a correlation between coronary artery disease and HDL-C (as the Examiner has noted) but also that "HDL-C levels are a strong graded and independent risk factor" (page 1, lines 24-25) while low HDL-C is associated with increased CAD risk even with normal plasma cholesterol levels (lines 26-28). The teaching on page 76 merely recognizes that a patient may exhibit low HDL-C prior to developing full blown cardiovascular disease although both can be parts of an overall pathological process and not alternative or mutually exclusive maladies so that this is not contrary to the other teachings of the application. As such, Applicants believe that the claims are well supported by these portions of the application.

Claims 24-28, 41-45, 49 and 57-62 were rejected under 35 U.S.C. §112, ¶1, as failing to meet the written description requirement on grounds that they contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner's argument is essentially that the claims, such as claim 24, are drawn to treating a disease by administering an agent that modulates ABC1 but that "the specification fails to disclose even a single representative species of the recited compounds that can be used for *in vivo* treatment of a mammal having or at risk of developing a cardiovascular disease." (See Office Action at page 7, lines 16-18)

In response, Applicants have amended claim 24, and thus the claims dependent therefrom, to delete reference to use of general agents and instead recite use of an agent that increases lipid transport activity of ABC1 in a mammal.

Because Applicants were the first to teach the physiological role of ABC1 there would have been no motivation for those in the art to provide ABC1 modulators for treatment of either HDL-C or the inevitably resulting cardiovascular diseases.

Claim 17 of U.S. Patent No. 6,617,122 provides a method "for identifying a compound that modulates human ABC1 polypeptide biological activity and is useful in modulating plasma cholesterol levels in a human...." (see the '122 at col. 210, lines 45-47)

Claim 21 of the '122 provides a method "for identifying a compound that modulates human ABC1 polypeptide biological activity for use in treating CAD...." (see the '122 at col. 210, lines 62-64)

Claim 23 of the '122 provides a method "for identifying a compound that modulates human ABC1 protein biological activity and is useful in modulating human plasma cholesterol levels...." (see the '122 at col. 211, lines 8-10)

In addition, Applicant's note that the written description requirement may be satisfied absent specific embodiments where the properties of the embodiments are adequately disclosed. (see, for example, MPEP §2163.06 (at page 2100-190), citing Union Oil. of Cal., 54 USPQ 2d 1227, 1232 (Fed. Cir. 2000)) Applicants further note that the present application is different from that considered in Univ. of Rochester v. G.D. Searle & Co., 69 USPQ 2d 1886 (Fed. Cir. 2004) because, in that case, the claims were drawn to a method of selectively inhibiting PGHS-2 activity by administering a compound that selectively inhibits such activity (which is tautomeric).

Conversely, in the present case, the obtainability of the required compounds is not in question because Applicants herein already have valid patent claims showing how to identify such compounds where the activity (modulating ABC1) was not previously known to be related to cardiovascular disease. Thus, Applicants herein are not claiming a

method for modulating ABC1 by contacting it with a modulator of ABC1 but, rather, a method for treating or preventing a disease by modulating a protein not previously known to regulate a key factor in cardiovascular disease.

In sum, Applicants have provided a method for treating or preventing cardiovascular disease by modulating ABC1 lipid transport activity (the present claims) and have provided a means for identifying agents useful in carrying out this activity (the parent '122 patent, with identical specification). Thus, Applicants have told those skilled in the art how to find such modulators and exactly what to do with them. The written description requirement is believed to have been satisfied.

Claims 24-28, 41-45, 49 and 57-62 were rejected under 35 U.S.C. §112, ¶1, as failing to meet the enablement requirement on grounds that they contain subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention.

In response, Applicants contend the following with respect to the Examiner's outline of the requirements of In re Wands:

1. Breadth of the claims

Applicants have amended claim 24, and thus the other claims that depend from it, to recite modulation specifically of the lipid transport activity of ABC1 and not just any biological activity. The Examiner notes that no direct modulation is recited and that any means of modulation is encompassed. However, Applicants urge that a specific mechanism of action of such modulation need not be recited. The claims are drawn to a method of treating cardiovascular disease, or risk of same, associated with low HDL-C by increasing ABC1-mediated lipid transport.

2. State of the Art and Level of Skill and Predictability

The Examiner notes that at the time of the invention, neither the specification nor the prior art disclosed a compound that modulates ABC1 activity and that could be used therapeutically to treat cardiovascular disease. He relies on Nofer et al (2005) as stating that such treatments may be on the horizon but that LXR agonists may cause detrimental gene changes. However, this is because LXRs are highly non-specific and act on many genes to up-regulate broad gene classes to cause detrimental effects.

Applicants respond that the advantage of the teaching of the application is in knowing the specific activity of ABC1 that is to be modulated. The relevant art is highly skilled and, knowing that ABC1 has a physiological role on HDL-C levels, based on cholesterol efflux, it is readily expected that agonists of this particular activity are the agents to be studied. That information was not known at the time the application was filed. For example, if cholesterol efflux and HDL binding of cholesterol are part of the ABC1 lipid transport activity (see application at page 28, lines 2-5, and at page 45) then clearly analogs of cholesterol and HDL are likely starting points. Given the advances of combinatorial chemistry and the specific screening assays already patented in the parent case, numerous compounds are readily prepared and tested. It should be noted that the claims are not drawn to a specific compound but rather to a way of treating cardiovascular disease associated with low HDL-C by modulating the lipid transport activity of ABC1.

3. Direction Provided by the Inventor and Working Examples

The Examiner contends that no specific compound is disclosed in the specification and that at the time of filing of the application no such useful compounds were known, although the Hamon et al. reference mentions glyburide as an inhibitor of ABC1-mediated anion transport.

Applicants reiterate their above remarks and add that the reason why useful compounds were not known is that the biological activities being screened for were of no use in treating cardiovascular disease. There is no evidence, for example, that cardiovascular disease is related to anion transport. Applicants' key invention is the determination of the physiological role of ABC1 in lipid, especially HDL-C, transport coupled with the already-established relationship between HDL-C and cardiovascular disease. Applicants readily concede that there may be many compounds that modulate some kind of ABC1 activity but modulating an activity like HDL-C transport is much more specific. The specification provides specific, cell-based screening assays for modulators, such as enhancers, of ABC1-mediated HDL-C transport and

4. Quantity of Experimentation Needed to Make or Use the Invention

The Examiner's comments are directed toward identifying all compounds that modulate any biological activity of ABC1. In response, Applicants first note that claim 24 was amended to recite modulation of lipid transport activity of ABC1 and no longer recites just any biological activity. In addition, as to any and all compounds being identified, because Applicants have identified the specific activity to be modulated (i.e., lipid transport) as well as the disease to be treated or prevented (i.e., cardiovascular disease associated with low HDL-C), the reactants and products of the reaction to be modulated have been identified. Thus, intracellular cholesterol is the "reactant" and extracellular HDL-cholesterol is the "product" of the biological reaction at hand. Applicants contend that putting such information into the hands of those skilled in the relevant art is sufficient to quickly generate useful materials for carrying out the invention. Anything beyond that is in the realm of regulatory agencies outside the patent field and Applicant has no control over the ultimate success of such a procedure.

Applicants also direct the Examiner's attention to the Bamberger patent (Ref. A1 in Applicants' Form 1449), U.S. 6,555,323 (a patent currently under reexamination), wherein

Table 1 of said patent identifies compounds that increase ABC1 activity (identified using essentially the same Assay as Applicants herein although Applicants herein are entitled to an earlier priority date than Bamberger).

Rejection Under 35 U.S.C. §102

Claims 24-28 and 42 were rejected under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) as being anticipated by Whitcomb (U.S. Patent 5,589,037) as evidenced by Nieland et al (2004). The Examiner's argument is that the claims "are drawn to a method for treating a mammal having or at risk of developing cardiovascular disease by administering to said mammal a compound that modulates ABCA1 biological activity." The Examiner notes that the '037 patent teaches that diabetes is often associated with cardiovascular disease and also teaches glyburide as a treatment for diabetes. Nieland et al (2004) teaches that glyburide modulates ABCA1-mediated cholesterol efflux from HEK cells and therefore treatment of a mammal with glyburide would meet the limitations of the claims.

In response, Applicants have amended claim 24 (and thus claims dependent from it) to recite that increasing ABC1-mediated lipid transport is to be the means of elevating HDL-C in a mammal having or at risk of developing cardiovascular disease (as supported throughout the application, for example, at page 1) The Whitcomb '037 patent does not appear to teach any connection between either cardiovascular disease or diabetes and low HDL-C.

Applicants also note that Nieland et al teaches glyburide as an inhibitor of ABCA1-mediated cholesterol efflux whereas Whitcomb (the '037) teaches that cholesterol levels were elevated over all treatments (see column 28, lines 32-33) and that HDL was elevated versus glyburide (column 28, lines 28-30). The '037 patent is not drwn to use of glyburide except merely as a positive control (see column 6, line 31). Further, if glyburide inhibits ABCA1-mediated cholesterol efflux (as Nieland teaches) then it would not be

responsible for the elevated HDL and cholesterol levels observed by Whitcomb and thus neither reference teaches use of glyburide to treat cardiovascular disease by modulating ABCA1. Indeed, Applicants' report (for example, at page 1 of the application) that HDL-C levels are inversely related to risk of coronary artery disease.

Whitcomb does not teach use of glyburide to treat cardiovascular disease (as evidenced by Nieland) because his results are at odds with Nieland, while Nieland's results are contrary to the relationship taught by Applicants. In sum, Whitcomb teaches use of glyburide as a control, does not teach use of glyburide for treating cardiovascular disease and the effects of glyburide would appear (based on Nieland) to be contrary to the desired result (as taught by Applicants) and to the amended claim 24 (which recites increase of lipid transport and not inhibition).

In fact, Applicants specifically disclose glyburide as an inhibitor of ABC1 (see application at page 55, line 11). Further, contrary to the Examiner's earlier assertion that the application discloses no modulators of ABC1, some upregulators of ABC1 are disclosed in the application at page 55, lines 14-16.

Claims 24-28, 42-43, 45 and 57-62 were rejected under 35 U.S.C. §102(a) or 35 U.S.C. §102(e), as being anticipated by Whitcomb (U.S. Patent 5,589,037) as evidenced by Nieland et al (2004) and further evidenced by Whitcomb (U.S. Patent 5,972,973). The Examiner reiterates his previous argument and adds that Whitcomb '973 teaches that the "classical manifestations of insulin resistance in a diabetic population are elevated triglycerides and low levels of HDL" [column 8, lines 29-31].

Applicants urge that the amendment of claim 24 to recite that the agent increases ABC1 lipid transport activity removes the cited references as anticipatory. In sum, Whitcomb '973 may teach increasing HDL levels but Applicants' teaching is that that means increasing ABC1 cholesterol efflux while Nieland et alteaches that glyburide inhibits ABC1 cholesterol efflux.

Claims 24-28, 42-43, 45 and 57-62 were rejected under 35 U.S.C. §102(a) or 35 U.S.C. §102(e), as being anticipated by Whitcomb (U.S. Patent 5,589,037) as evidenced by Nieland et al (2004) and further evidenced by Cooper at al. (U.S. Patent 5,260,275). The Examiner reiterates his previous argument and adds that Cooper '275 teaches that the "major cause of death and disability in diabetes is coronary artery disease" [column 2, at the top].

In response, Applicants again urge that the amendment of claim 24 to recite that the agent increases ABC1 lipid transport activity removes the cited references as anticipatory. Cooper '275 allegedly teaches treating CAD by treating diabetes but he does not relate either to ABC1 and the only treatment mentioned by the Examiner is glyburide, which decreases (not increases) ABC1-mediated cholesterol efflux (contrary to Nieland et al, which teaches that glyburide inhibits ABC1 cholesterol efflux).

Claims 24-28, 42-43, 45 and 57-62 were rejected under 35 U.S.C. §102(b) or 35 U.S.C. §103, as being anticipated or rendered obvious by the teaching of Kamai et al (1994) as evidenced by Nieland et al (2004) and Whitcomb (U.S. Patent 5,589,037). The Examiner cites Kamei et al as teaching administration of glyburide to a diabetic mouse.

In response, Applicants again refer to the amendment of claim 24 to recite use of an agent that increases ABC1 lipid transport whereas Nieland et al teach that glyburide decreases ABC1 cholesterol efflux.

In view of the amendments to the claims and the above remarks, Applicants believe that the grounds of rejection have been overcome and request reconsideration of the pending claims.

Obviousness-Type Double Patenting

Claims 24-28, 42-43, 45 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over U.S. utility applications 10/479,198, 10/744,465, 10/745,377 and 10/833,679.

Claims 24-28, 42-43, 45 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over claims 23, 24, 26 and 27 of U.S. utility applications 10/479,198. The indicated claims are drawn to use of a modulator that was first identified in an assay involving contacting the compound with a polynucleotide containing a polymorphism in a non-coding region to promote expression of ABC1.

In response, Applicants have included herewith a Terminal Disclaimer, which is believed to obviate this ground of rejection.

Claims 24-28, 42-43, 45 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over claims 36-45 of U.S. utility applications 10/744,465. The indicated claims are drawn to a method of treating a disease or disorder in an mammal comprising administering to a mammal so afflicted an effective amount of a compound identified as a modulator of ABCA1 using a screening assay based on an ABC1 expression system, with and without a reporter gene. The indicated agents would thus not affect ABC1 polypeptide directly.

In response, Applicants have included herewith a Terminal Disclaimer, which is believed to obviate this ground of rejection.

Claims 24-28, 42-43, 45 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over claims 26-28 and 32 of U.S. utility applications 10/745,377.The indicated claims are drawn to a method of treating a condition in an animal (which includes cardiovascular disease) comprising administering

to an animal afflicted therewith a therapeutically effective amount of an agent that has HDL-level modulating activity in an assay based on LXR modulation. Again, such compounds would affect expression of ABC1 and not the polypeptide itself. Applicants' claims herein are drawn to increasing lipid transport activity of the ABC1 polypeptide.

In response, Applicants have included herewith a Terminal Disclaimer, which is believed to obviate this ground of rejection.

Claims 24-28, 42-43, 45 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over claims 36-48 of U.S. Application 10/833,679. The indicated claims are drawn to treating low HDL cholesterol or cardiovascular disease by administering a nucleic acid molecule encoding an ABC1 polypeptide or a cholesterol-regulating fragment thereof. In response, Applicants note that claim 24 (and thus all claims dependent thereon) has been amended to recite that the compound increases lipid transport activity of an ABC1 polypeptide whereas the cited application has claims drawn to administering a nucleic acid that would, presumably, encode more ABC1 polypeptide. Applicants' pending claims herein (claim 24 and claims dependent thereon) are not drawn to such an embodiment and therefore are believed not obvious over the cited claims.

Finally, Applicants are not aware of any additional pending patent applications that claim subject matter similar to that of the claims herein. In addition, Applicants have submitted herewith some additional references on Form 1449 plus an Informational Disclosure Statement and the appropriate fee.

The Commissioner is authorized to charge payment of any fees required for this communication or credit any overpayment to Deposit Account No. 03-0678.

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Alan J. Grant , Esq. **Date**

Respectfully submitted,

Alan J. Grant

Alan J. Grant, Esq.
Reg. No. 33,389

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
5 Becker Farm Road
Roseland, NJ 07068
Phone: 973-994-1700
Fax: 973-994-1744